Original Study

Effect of Metformin on Sleep Disorders in Adolescent Girls with Polycystic Ovarian Syndrome

Ahmed A. El-Sharkawy MD [1], Ghada S. Abdelmotaleb MD [1], Mohammed K. Aly MD [1,*], Ahmed M. Kabel [2]

[1] Pediatric Department, Faculty of Medicine, Benha University, Benha, Egypt
[2] Faculty of Medicine, Tanta University, Tanta, Egypt

A B S T R A C T

Objective: Patients with polycystic ovarian syndrome (PCOS) have a high prevalence of sleep disorders. Metformin is an antidiabetic drug that may have a role in treatment of the manifestations of PCOS. The aim of this study was to assess the presence of sleep disorders in adolescent girls with PCOS and to study the effects of using metformin on sleep disorders in these girls.
Methods: This study was carried out on 90 adolescent girls aging from 12 to 18 years who were divided into 3 equal groups: control untreated group, untreated PCOS group, and PCOS + metformin group. Body weight, height, body mass index, hirsutism score, fasting and postprandial blood glucose, fasting serum insulin, Homeostatic Model Assessment (HOMA) index, sleep disturbances scale, and Epworth sleepiness scale were measured.
Results: Metformin administration resulted in significant decrease in the body weight, body mass index, hirsutism score, fasting and postprandial blood glucose, fasting serum insulin, HOMA index, sleep disturbances scale, and Epworth sleepiness scale compared to the untreated PCOS group.
Conclusion: Metformin can reduce the incidence of sleep disorders and excessive daytime sleepiness in adolescent girls with PCOS.
Key Words: Metformin, Sleep, Adolescent, PCOS

Introduction

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age. The prevalence of PCOS depends on the choice of diagnostic criteria. One community-based prevalence study using the Rotterdam criteria found that about 18% of women had PCOS and that 70% of them were previously undiagnosed.[1] It usually presents at puberty with irregular menstrual cycles, signs of hyperandrogenism, such as acne and hirsutism, and insulin resistance.[2]

The biochemical features of PCOS include elevated serum testosterone levels, elevated luteinizing hormone (LH) levels, and elevated LH/follicle-stimulating hormone (FSH) ratios. The prevalence of obesity in PCOS is as high as 75%.[3] Patients with PCOS are at increased risk for developing reproductive, metabolic and cardiovascular disorders, including infertility, insulin resistance, diabetes mellitus type 2, hypertension, and atherosclerosis.[4]

Recent studies showed that PCOS is associated with sleep disorders including sleep-disordered breathing as well as with excessive daytime sleepiness (EDS). In fact, a prospective case-control study estimated that women with PCOS have a 30-fold higher prevalence of sleep disorders than women in the general population.[5]

The pathophysiological mechanisms leading to this high prevalence of sleep disorders in PCOS have not yet been identified. However, possible causes include alterations in body fat composition due to excess androgen levels and/or the effects of the metabolic syndrome,[6] the latter of which was previously associated with an increased risk of sleep disorders in patients without PCOS.[7] Even though sleep disorders are highly prevalent in women with the disorder, the history of this disorder in adolescent girls and young women is unknown, mainly due to lack of knowledge about such an association.[8]

Metformin is emerging as an important component of PCOS treatment. In addition to the expected improvement in insulin sensitivity and glucose metabolism, metformin therapy also ameliorates hyperandrogenism and menstrual irregularity.[9] Although most studies of metformin have involved obese PCOS women, non-obese PCOS patients profit from treatment as well. Moreover, metformin appears to be more effective in adolescents with PCOS than for adults with PCOS. Also, metformin improves the lipid profile in PCOS adolescents and decreases C-reactive protein levels, which are predictive to cardiovascular disease.[10] However, there are few studies concerning the effect of metformin on sleep disorders in PCOS. The aim of this study was to assess the presence of sleep disorders in adolescent girls with PCOS and to study the effects of metformin on sleep disorders in these girls.

Patients and Methods

This study was carried out on adolescent girls aging from 12 to 18 years who attend to Pediatric Clinic, Benha

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* *Address correspondence to:* Mohammed Khaled Aly, MD, Department of Pediatrics, Faculty of Medicine, Benha University, Benha, Egypt; PC 13511; Phone: +201009041488.
E-mail address: dra_kabel@yahoo.com (M.K. Aly).

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Table 1
Baseline Characteristics of the Patients Included in this Study

	Control		Untreated PCOS		PCOS + Metformin	
	Range	mean ± SEM	Range	mean ± SEM	Range	mean ± SEM
Age (Years)	13.5–17.5	15.7 ± 0.12	13.2–17.9	15.9 ± 0.36[c]	13.7–17.8	16.2 ± 0.7[a,b]
Body weight (kg)	46.32–61.51	51.45 ± 1.44	65.4–85.67	78.81 ± 2.13[a]	64.21–83.96	75.89 ± 1.45[a,b]
BMI	18.34–24.11	21.47 ± 0.55	32.45–39.5	35.25 ± 0.73[a]	31.89–37.87	34.23 ± 0.51[a,b]
Fasting blood glucose (mg/dl)	75.43–92.67	86.5 ± 1.65	118.9–137.8	125.23 ± 2.61[a]	116.3–135.23	121.76 ± 3.57[a,b]
Postprandial blood glucose (mg/dl)	105.47–124.2	115.64 ± 1.64	143.3–167.11	161.58 ± 2.19[a]	142.2–165.7	159.84 ± 2.19[a,b]
Fasting serum insulin (mU/l)	5.04–6.23	5.3 ± 0.42	14.23–21.56	18.5 ± 0.82[a]	13.67–20.98	17.81 ± 0.69[a,b]
HOMA index	1.51–1.94	1.78 ± 0.12	2.92–3.59	3.28 ± 0.13[a]	2.87–3.52	3.11 ± 0.12[a,b]
Hirsutism score	5–9	7.73 ± 0.51	16–25	22.15 ± 1.34[a]	17–26	23.92 ± 0.85[a,b]
Sleep disturbances scale	35–59	48.22 ± 1.13	64–88	75.87 ± 2.56[a]	65–85	78.64 ± 1.86[a,b]
Epworth sleepiness scale	5–10	8.18 ± 0.41	10–18	15.93 ± 0.61[a]	11–18	16.75 ± 0.52[a,b]

[a] Significant compared to the control group.
[b] Non significant compared to untreated PCOS group.
[c] Non significant compared to the control group.

University Hospital, Benha University, Egypt. All patients were post-menarcheal at the time of inclusion in the study. This study was approved by the local ethics committee.

Inclusion Criteria

Patients with aged 12 to 18 years without abnormal pretreatment laboratory studies (Abnormal liver or renal function tests) were included in this study. Every patient was evaluated for diagnosis of PCOS according to the Rotterdam Criteria.[11] These include evaluation of the patients for the presence of menstrual irregularity, clinical evidence of hyperandrogenism such as acne or hirsutism and suggestive features of PCOS by pelvic-abdominal ultrasonography. These features included the presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter and/or increased ovarian volume (more than 10 cm^3). Girls showing at least 2 of these evaluations were considered adequately evaluated for PCOS.

Exclusion Criteria

Patients having any chronic diseases such as hypertensive and hepatic patients and those having malignancy or congenial adrenal hyperplasia.

Study Groups

This study was carried out on 90 female patients who were divided into 3 equal groups as follows:

The first group was untreated PCOS patients.

The second group was PCOS patients who were randomly assigned to receive metformin tablets in a dose of 850 mg twice daily orally for 3 months.[12]

The third group was the normal control untreated group.

All included patients were subjected to a full history taking with stressing on demographic data including: age, sex, residence, and consanguinity, menstrual history, and similar conditions in the family.

The patients were evaluated for anthropometric measurements including weight, height and body mass index (BMI) calculated as kg/m^2. Hirsutism score was calculated using a modification of Ferriman-Gallwey scoring system.[13] Ovarian examination was done by pelvic-abdominal ultrasonography. Fasting and 2 hours postprandial blood glucose levels were measured using commercially available kits supplied by Diamond-Diagnostics (Holliston, MA) according to the method of Trinder.[14] Fasting serum insulin was measured using ELISA kits supplied by DRG Diagnostics, Marburg, Germany, according to the method of Gallois et al.[15] The Homeostatic Model Assessment (HOMA) index, defined as the normalized product of fasting glucose and fasting insulin levels and used as a measure of insulin resistance, was calculated from available insulin and glucose levels as follows: HOMA = fasting glucose (mg/dL) X fasting insulin (mU/mL)/405.[16] The baseline characteristics of the patients included in this study are shown in Table 1. Also, ENT examination was performed to exclude the presence of organic cause of sleep disorders. The PCOS patients treated with metformin received counseling regarding life style changes including regular daily exercise and dietary changes.

Screening for Sleep Disorders

Screening was carried out by using the sleep disturbances scale.[17] This scale consists of 26 items that determine the presence of disorders of initiating and maintaining sleep, sleep breathing disorders, disorders of arousal, sleep-wake transition disorders, disorders of excessive somnolence, and sleep hyperhydrosis. This was rated on a scale of 1 (Never) to 5 (daily). The total score ranges from 26-130, with a score more than 52 considered positive for sleep disorders.

Screening for Excessive Daytime Sleepiness

EDS was identified using a modified version of the Epworth Sleepiness Scale.[18] The probability of falling asleep in 8 different situations was rated on a scale of 0 (not likely at all) to 3 (extremely likely). The total score ranges from 0-24, with a score more than 10 considered positive for EDS.

Statistical Analysis

For statistical analysis, the SPSS (version 16.0) package program was used. Parameters were shown with mean ± SEM. To compare the differences among groups, a Student

Table 2
Body Weight, BMI, Fasting and Postprandial Blood Glucose, Fasting Serum Insulin, HOMA Index and Hirsutism Score in the Different Groups at the End of the Study

	Control		Untreated PCOS		PCOS + Metformin	
	Range	mean ± SEM	Range	mean ± SEM	Range	mean ± SEM
Body weight (kg)	45.53–62.11	50.45 ± 1.87	66.5–86.34	77.8 ± 1.55[a]	52.9–68.2	57.21 ± 1.01[b]
BMI	17.94–23.91	20.97 ± 0.46	31.65–39.4	36.28 ± 0.81[a]	24.4–32.56	26.18 ± 0.43[b]
Fasting blood glucose (mg/dl)	76.4–91.69	84.6 ± 1.83	119.2–139.8	128.66 ± 1.87[a]	92.6–122.4	96.85 ± 1.92[b]
Postprandial blood glucose (mg/dl)	108.5–126.2	119.64 ± 1.34	144.5–169.1	165.02 ± 1.76[a]	124.3–148.6	128.56 ± 0.79[b]
Fasting serum insulin (mU/l)	5.03–6.33	5.4 ± 0.32	15.13–22.5	18.9 ± 0.86[a]	8.45–15.14	10.8 ± 0.7[b]
HOMA index	1.47–2.01	1.83 ± 0.11	2.86–3.34	3.24 ± 0.23[a]	2.03–2.94	2.31 ± 0.09[b]
Hirsutism score	5–9	7.45 ± 0.44	18–28	25.05 ± 1.2[a]	13–22	16.85 ± 0.88[b]

[a] Significant compared to the control group.
[b] Significant compared to untreated PCOS group.

t test was used for parametric analysis. Pearson's correlation coefficient (r) was applied to correlate between the parameters. Data were considered statistically significant if $P < 0.05$.

Results

Effect of Metformin on Body Weight and BMI (Table 2)

In untreated PCOS patients, there was significant increase in the body weight and BMI compared to the control untreated group. In PCOS patients treated with metformin, there was significant decrease in the body weight and BMI compared to the untreated PCOS patients and compared to the baseline characteristics of this group before treatment.

Effect of Metformin on Fasting and Postprandial Blood Glucose (Table 2)

In untreated PCOS patients, there was significant increase in fasting and postprandial blood glucose compared to the control untreated group. In PCOS patients treated with metformin, there was significant decrease in fasting and postprandial blood glucose compared to the untreated PCOS patients and compared to the baseline characteristics of this group before treatment.

Effect of Metformin on Fasting Serum Insulin and HOMA Index (Table 2)

In untreated PCOS patients, there was significant increase in fasting serum insulin and HOMA index compared to the control untreated group. In PCOS patients treated with metformin, there was significant decrease in fasting serum insulin and HOMA index compared to the untreated PCOS patients and compared to the baseline characteristics of this group before treatment.

Effect of Metformin on the Hirsutism Score (Table 2)

In untreated PCOS patients, there was significant increase in the hirsutism score compared to the control untreated group. In PCOS patients treated with metformin, there was significant decrease in the hirsutism score compared to the untreated PCOS patients and compared to the baseline characteristics of this group before treatment.

Effect of Metformin on the Sleep Disturbances Scale (Table 3)

In untreated PCOS patients, there was significant increase in the sleep disturbances scale compared to the control untreated group. In PCOS patients treated with metformin, there was significant decrease in the sleep disturbances scale compared to the untreated PCOS patients and compared to the baseline characteristics of this group before treatment.

Effect of Metformin on the Epworth Sleepiness Scale (Table 3)

In untreated PCOS patients, there was significant increase in the Epworth sleepiness scale compared to the control untreated group. In PCOS patients treated with metformin, there was significant decrease in the Epworth sleepiness scale compared to the untreated PCOS patients and compared to the baseline characteristics of this group before treatment.

Correlation between the Different Parameters and the Sleep Disturbances Scale (Table 4)

There was significant positive correlation ($P < .05$) between body weight, body mass index, fasting and postprandial blood glucose, fasting serum insulin, HOMA index, hirsutism score, and the sleep disturbances scale in cases with PCOS.

Table 3
Sleep Disturbances Scale and Epworth Sleepiness Scale in the Different Groups at the End of the Study

	Control		Untreated PCOS		PCOS + Metformin	
	Range	mean ± SEM	Range	mean ± SEM	Range	mean ± SEM
Sleep disturbances scale	34–58	46.45 ± 1.06	63–89	81.10 ± 2.07 [a]	51–69	63.75 ± 1.45[b]
Epworth sleepiness scale	5–9	8.1 ± 0.44	11–19	17.3 ± 0.59 [a]	8–14	12.1 ± 0.56[b]

[a] Significant compared to the control group.
[b] Significant compared to untreated PCOS group.

Table 4
Correlation between Body Weight, Body Mass Index, Fasting, and Postprandial Blood Glucose, Fasting Serum Insulin, HOMA Index, Hirsutism Score and Sleep Disturbances Scale in Cases with PCOS at the End of the Study

Sleep Disturbances Scale Variables	Pearson r-Value	*P*-Value
Body weight	0.685	<.05
Body mass index	0.735	<.05
Fasting blood glucose	0.563	<.05
Postprandial blood glucose	0.696	<.05
Fasting serum insulin	0.538	<.05
HOMA index	0.654	<.05
Hirsutism score	0.564	<.05

Correlation between the Different Parameters and the Epworth Sleepiness Scale (Table 5)

There was significant positive correlation ($P < .05$) between body weight, body mass index, fasting and postprandial blood glucose, fasting serum insulin, HOMA index, hirsutism score, and the Epworth sleepiness scale in cases with PCOS.

Discussion

Polycystic ovary syndrome is one of the most common endocrine disorders in females of the reproductive age worldwide. The major endocrine disruption is excessive androgen secretion and a large proportion of females also have abnormal insulin activity. This reflects the increased incidence of PCOS in adolescent females because of the hormonal and metabolic changes that occur during puberty and may influence the pathogenesis of PCOS.[19,20]

Many studies have shown that patients with PCOS have a significantly higher prevalence of sleep disorders compared to healthy individuals. This was attributed to that the main features of PCOS including obesity, insulin resistance, and hyperandrogenemia are believed to contribute to the pathogenesis of sleep disorders.[21] Obesity found in PCOS may increase the resistive load on the upper airway during sleep leading to obstructive sleep apnea. Moreover, sleep disorders may induce and exaggerate insulin resistance. Studies evaluating the relationship between PCOS and sleep disorders in adolescent girls are still very limited.[22]

In the present study, the untreated PCOS patients show significant increase in the body weight, BMI, hirsutism score, fasting and postprandial blood glucose, fasting serum insulin, HOMA index, sleep disturbances scale, and the Epworth sleepiness scale compared to the control untreated group. These results were in agreement with Azziz et al,[4] Broder-Fingert et al,[11] Hannon et al,[7] and Nandalike et al.[22]

Trent et al[23] reported that adolescents with PCOS are more likely to be overweight than their healthy peers. Recent studies demonstrated that BMI is significantly elevated in adolescent girls with PCOS compared to their peers. Weight status is considered as an important mediator in the relationship between PCOS and health-related quality of life in adolescent girls with the disorder.[11]

There is a strong evidence that growth patterns in early life are associated with risk of the metabolic syndrome in adulthood. Obesity in adolescents may lead to changes in the hypothalamic-pituitary axis, insulin secretion and sensitivity.[24] Moreover, obesity was believed to predispose to the metabolic and endocrinal changes which occur in PCOS including impaired glucose tolerance, insulin resistance, dyslipidemia, decreased leptin secretion, menstrual irregularities, and infertility.[19]

Insulin resistance, manifested by elevated levels of the fasing and postprandial blood glucose, fasting serum insulin, and HOMA index, is the most common metabolic abnormality in PCOS patients with an incidence of 71% followed by obesity (52%) and dyslipidemia (46.3%).[25] The proposed mechanisms are peripheral target tissue resistance, decreased hepatic clearance, and increased pancreatic sensitivity.[19] Many studies suggested that insulin resistance in PCOS patients may be due to dysregulation of insulin receptor phosphorylation which leads to inhibition of the normal signaling and a significant decrease in insulin responsiveness.[26] Also, this appears to increase the activity of P450c17α, the key regulatory enzyme in androgen biosynthesis. Polymorphisms in the genes involved in insulin secretion or insulin receptor metabolism have also been implicated in the aetiology of insulin resistance. Moreover, Witchel et al[27] hypothesized that the hyperandrogenemic endocrine environment during puberty has a profound effect on body fat distribution predisposing to insulin resistance.

Hyperinsulinemia and insulin resistance had been proposed as the primary events leading to hyperandrogenism. Insulin stimulates ovarian androgen production by direct and indirect mechanisms.[28] Nelson et al[29] reported that insulin may act by stimulation of cytochrome P450c17α activity in the ovaries or adrenals of women with PCOS, thus affecting steroidogenesis. Insulin also binds to the insulin-like growth factor 1 receptors on the ovary, thereby modulating ovarian steroidogenesis leading to excessive androgen production.[30] Also, long-term hyperinsulinemia was proven to stimulate leptin secretion. Dogan and Gulekli[31] reported that there is a significant correlation between leptin and LH concentrations suggesting a possible involvement of leptin in LH hypersecretion and hyperandrogenism.

Hirsutism is one of the clinical manifestations of hyperandrogenism which is prevalent in more than 70% of females with PCOS. Allahbadia and Merchant[19] reported that insulin resistance may result in suppression of sex hormone binding globulin, elevation of free biologically active testosterone and the final manifestation of hirsutism.

Table 5
Correlation between Body Weight, Body Mass Index, Fasting and Postprandial Blood Glucose, Fasting Serum Insulin, HOMA Index, Hirsutism Score and the Epworth Sleepiness Scale in Cases with PCOS at the End of the Study

Epworth Sleepiness Scale Variables	Pearson r-Value	*P*-Value
Body weight	0.605	<.05
Body mass index	0.585	<.05
Fasting blood glucose	0.623	<.05
Postprandial blood glucose	0.696	<.05
Fasting serum insulin	0.486	<.05
HOMA index	0.521	<.05
Hirsutism score	0.455	<.05

Genetic differences in the activity of the 5-α reductase enzyme which converts testosterone to dihydrotestosterone may modify the degree of hirsutism. Insulin and insulin-like growth factors were proven to stimulate 5-α reductase activity leading to increased incidence of hirsutism.[32]

Vgontzas et al[33] reported a higher prevalence of sleep disorders in females with PCOS compared with the general population, and found that insulin resistance was the strongest predictor for sleep disorders when adjusted for age, BMI, and testosterone levels. Tasali et al[6] reported that higher fasting glucose levels are detected in young women with PCOS and sleep disorders. These studies were in agreement with the results of the present study where there was significant positive correlation between body weight, body mass index, fasting and postprandial blood glucose, hirsutism score, fasting serum insulin, HOMA index, and each of sleep disturbances scale and Epworth sleepiness scale.

Many studies have linked metabolic syndrome that is commonly found in PCOS to sleep disorders.[7] The mechanisms may be related to increased abdominal visceral obesity, which alters chest wall and upper airway movements and reduces functional residual capacity, increasing the risk of hypoxia during sleep.[5] This is in accordance with the results of the present study where there was significant positive correlation between body weight and BMI on one side and sleep disturbances scale and Epworth sleepiness scale on the other side. Also, it has been shown that sleep disorders can induce metabolic syndrome by decreasing insulin sensitivity.[34] Tasali et al[6] reported that treatment of sleep disorders in PCOS patients with continuous positive airway pressure leads to improvement of the manifestations of metabolic syndrome.

Hyperandrogenemia is another possible factor explaining the high prevalence of sleep disorders in PCOS. Differences in androgen levels may affect body composition, visceral adiposity, upper airway anatomy, and ventilatory drive during sleep and insulin resistance.[22] These studies are in line with the results of the present study where there was significant positive correlation between hirsutism score, which indicates hyperandrogenism, and both the sleep disturbances scale and the Epworth sleepiness scale.

In contrast to the findings of the present study, de Sousa et al[21] found no differences in the prevalence of sleep disorders in adolescents with PCOS compared with normal and obese controls. Such differences between studies could be related to different methodologies as well as to different sample size and populations.

The present study indicated that excessive daytime sleepiness (EDS), manifested by significant increase in the Epworth sleepiness scale, was more prevalent in the PCOS group compared to the control group. This finding is consistent with previous reports of EDS in adolescent girls with PCOS.[5] Various factors might explain the presence of EDS in PCOS patients, including sleep deprivation secondary to sleep disorders. Other causes include insomnia with poor sleep efficiency. Also, the psychological stress and neurohormonal imbalances resulting from PCOS may predispose to EDS.[21] This was in agreement with the results of the present study where there was significant positive correlation between body weight, BMI, fasting and postprandial blood glucose, fasting serum insulin, HOMA index, hirsutism score, and the Epworth sleepiness scale.

Metformin is an oral antidiabetic drug that is considered as the first-line of choice for treatment of type 2 diabetes, especially in overweight patients. It is also used in treatment of PCOS and has been investigated for other diseases where insulin resistance may be the underlying factor. Metformin works by decreasing intestinal absorption of glucose, suppressing glucose production by the liver, increasing glucose utilization by the extrahepatic tissues, decreasing insulin resistance, decreasing glucagon secretion, and improving the lipid profile in PCOS. Metformin appears to be more effective in adolescents with PCOS than for adults with the same disorder.[10,35]

In the present study, PCOS patients treated with metformin show significant decrease in the body weight, BMI, hirsutism score, fasting and postprandial blood glucose, fasting serum insulin, HOMA index, sleep disturbances scale, and Epworth sleepiness scale compared to the untreated PCOS patients and compared to the baseline characteristics of this group before treatment. These results were in agreement with Ibanez et al,[10] Shaker et al,[12] and Tang et al.[36]

The beneficial effects of metformin in PCOS are based on alleviation of insulin excess acting upon the ovary and through direct ovarian effects. Metformin improves insulin sensitivity leading to reduction of CYP17 activity leading to inhibition of ovarian steroidogenesis. Furthermore, metformin suppresses androstenedione production by a direct effect on ovarian theca cells and decreases FSH-stimulated aromatase activities in females with PCOS.[37] Moreover, metformin leads to reduction of body weight which improves the manifestations of PCOS.[36] Ibanez et al[10] reported that early metformin therapy (age 8-12 y) in girls with precocious pubarche can reduce hirsutism, androgen excess, and oligomenorrhea in adolescence.

The molecular pathways whereby metformin acts directly on the ovary remain elusive. It had been demonstrated that metformin treatment increased AMP-activated kinase activity in the granulosa cells, leading to subsequent reduction of steroid synthesis.[37] Moreover, metformin has been shown to reduce the risks of abortion in women with PCOS at high risk of pregnancy and neonatal complications by increasing some factors needed for implantation and pregnancy maintenance and improving the uterine arterial blood flow. These effects may be mediated by the metformin-induced improvement in insulin sensitivity.[38]

The relationship between metformin and sleep disorders in PCOS remain controversial. Nandalike et al[5] reported that metformin might decrease the prevalence of sleep disorders and EDS in adolescent girls with PCOS by lowering the predisposing factors for the development of sleep disorders and EDS in these patients. These include reduction of body weight, prevention of hyperandrogenemia, improvement of glucose tolerance, and inhibition of insulin resistance. A study carried out by Ramadan et al[39] found that sleep apnea induced by high-fat diet can be reversed and prevented by metformin.

On the other hand, there are many reports that metformin can produce some types of sleep disorders, especially insomnia and sleep walking. The cause is still uncertain but the changes in blood glucose levels that may occur after starting therapy with metformin might be a possible mechanism.[40]

Conclusion

Metformin can reduce the incidence of sleep disorders and EDS in adolescent girls with PCOS. The mechanisms may include reduction of BMI, decreased androgen production, improvement of glucose tolerance, and inhibition of insulin resistance. We recommend that metformin can be used as adjuvant agent for management of sleep disorders in adolescent girls with PCOS and further studies are needed to explore the molecular mechanisms by which metformin can affect sleep disorders.

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